(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 July 2005 (21.07.2005)

PCT

(10) International Publication Number
WO 2005/066120 A2

(51) International Patent Classification[7]: C07D 205/00

(21) International Application Number:
PCT/IB2004/004281

(22) International Filing Date:
23 December 2004 (23.12.2004)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1643/Del/2003 30 December 2003 (30.12.2003) IN

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: PROCESS FOR ASYMMETRIC SYNTHESIS OF HYDROXY-ALKYL SUBSTITUTED AZETIDINONE DERIVATIVES OF INTERMEDIATES THEREOF

(57) Abstract: Provided herein are processes for asymmetric synthesis of hydroxyalkyl-substituted azetidinone derivatives or intermediates thereof via stereoselective reduction of benzylic ketone using (-)-B-chlorodiisopinocampheylborane. Also provided herein are processes for preparing ezetimibe.

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PROCESS FOR ASYMMETRIC SYNTHESIS OF HYDROXY-ALKYL SUBSTITUTED AZETIDINONE DERIVATIVES OF INTERMEDIATES THEREOF

Field of the Invention

Provided herein are processes for asymmetric synthesis of hydroxyalkyl-substituted azetidinone derivatives or intermediates thereof via stereoselective reduction of benzylic ketone using (-)-B-chlorodiisopinocampheylborane. Also provided herein are processes for preparing ezetimibe.

Background of the Invention

Hydroxyalkyl substituted azetidinone derivatives, such as ezetimibe, *i.e.*, 1-(4-fluorophenyl)-3-(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, are useful as hypocholesterolemic agents in the prevention and treatment of atherosclerosis. U.S. Patent No. 5,767,115 discloses hydroxy-substituted azetidinones as useful hypocholesterolemic agents in the treatment or prevention of atherosclerosis. Several processes have been reported for the preparation of diphenylazetidinones, such as in U.S. Patent Nos. 5,631,365; 5,886,171; 6,207,822; 6,133,001; and 5,856,473.

Stereoselective microbial reduction of 1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl)]-4-(S)-(4-hydroxyphenyl)-2-azetidinone to 1-(4-fluorophenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl)propyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone using *Rhodococcus fascians* ATCC No. 202210 or fungal isolate *Geotrichum candidum* ATCC No. 74487 is disclosed in U.S. Patent No. 6,133,001. Stereoselective microbial reduction of 3-[5-(4-fluorophenyl)-5-oxopentanoyl]-4(S)-4-phenyl-1,3-oxazolidin-2-one to 3-[(5*S*)-5-(4-fluorophenyl)-5-hydroxypentanoyl]-4(S)-4-phenyl-1,3-oxazolidin-2-one using culture broth of *Schizosaccharomyces octosporus* ATCC 2479 is disclosed in U.S. Patent No. 5,618,707. Culture broth of *Zygosaccharomyces bailii* ATCC 38924 is disclosed as being useful in stereoselective microbial reduction of 5-(4-fluorobenzoyl)-5-oxopentanoic acid to obtain (5S)-5-(4-fluorophenyl)-5-hydroxypentanoic acid in U.S. Patent No. 5,618,707.

U.S. Patent Nos. 5,886,171 and 5,856,473 disclose chiral reduction of protected 1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl)]-4(S)-(4-hydroxyphenyl)-2-

azetidinone to protected 1-(4-fluorophenyl)-3(R)-[3(S)-hydroxy-3-(4-fluorophenyl)propyl)]-4(S)-(4-hydroxyphenyl)-2-azetidinone with borane dimethylsulfide complex, borane tetrahydrofuran complex or sodium borohydride by using a chiral catalyst such as one shown in Figure I

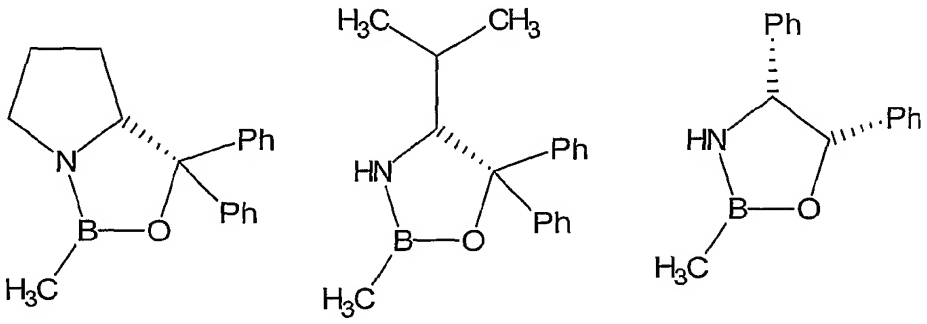
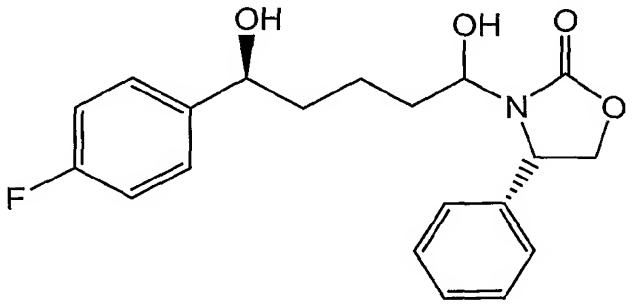


FIGURE I

U.S. Patent No. 6,207,822 discloses the use of similar reducing agents and chiral catalyst for reduction of 3-[5-(4-fluorophenyl)-5-oxopentanoyl]-4(S)-4-phenyl-1,3-oxazolidin-2-one to 3-[(5*S*)-5-(4-fluorophenyl)-5-hydroxypentanoyl]-4(S)-4-phenyl-1,3-oxazolidin-2-one. U.S. Patent No. 6,627,757 and *Tetrahedron Letters*, 2003, 44, 801 disclose a similar reduction with borane tetrahydrofuran complex by using (R)-tetrahydro-1-methyl-3,3-diphenyl-1H,3H-pyrrolo(1,2-c)(1,2,3)-oxazaborolidine [(R)-MeCBS] or R-diphenylprolinol as a catalyst.

The enantioselectivity of the reduction step depends on the rate and mode of addition of borane-complex, moisture sensitivity of the reaction medium and temperature. Reduction with borane tetrahydrofuran or borane dimethylsulfide using a chiral catalyst leads to problems associated with the formation of over-reduced products, such as compound of Formula A

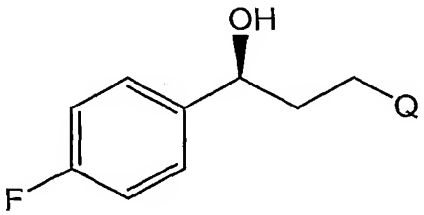


Formula A

and handling of borane gas at large scale, which is used for making borane-complex. Accordingly, there is a need for an alternate, commercially viable, environment-friendly and efficient enantioselective method of preparing hydroxyalkyl-substituted azetidinone derivatives.

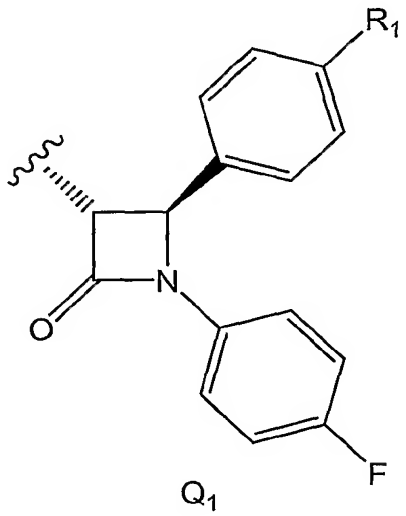
Summary of the Invention

Generally provided herein are processes for the preparation of compounds of Formula I



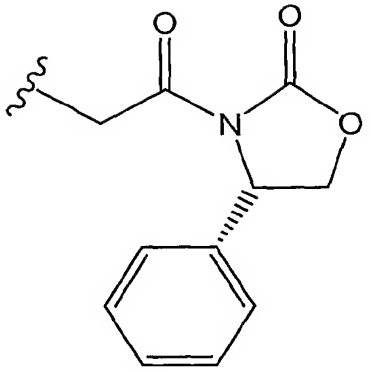
Formula I

wherein Q represents Q_1



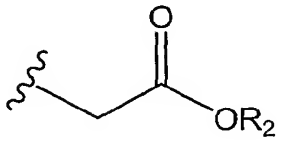
Q_1

(wherein R_1 can be hydroxy or protected hydroxy group), Q_2,



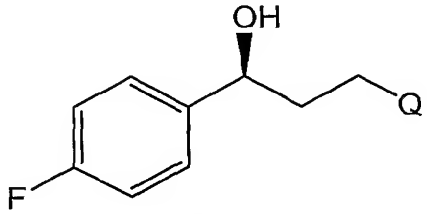
Q_2

or Q_3, wherein R_2 can be an alkyl, aryl or aralkyl group.



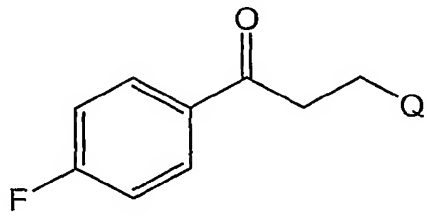
Q_3

In particular, provided herein are processes for the preparation of a compound of Formula I,



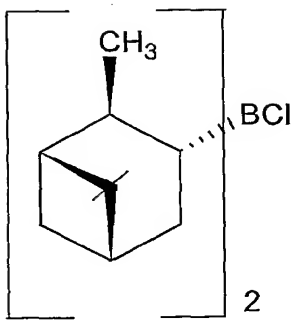
Formula I

comprising reducing the compound of Formula II,



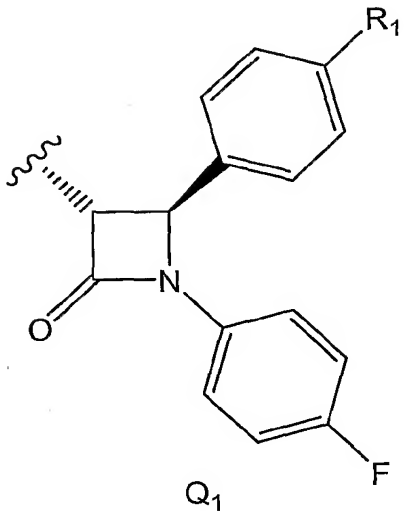
Formula II

with (-)-B-chlorodiisopinocampheylborane of Formula III

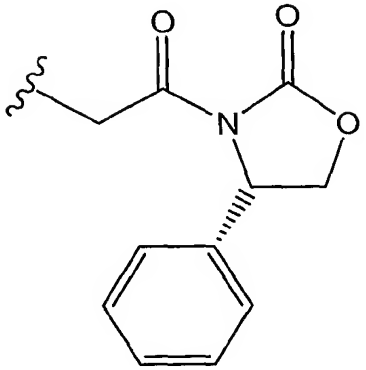


Formula III

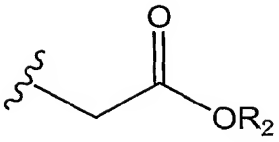
wherein Q is Q_1, Q_2, or Q_3,



Q_1



Q_2

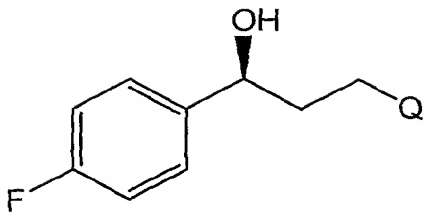


Q_3

and wherein R_1 is hydroxy or a protected hydroxy group and R_2 is an alkyl, aryl or aralkyl group.

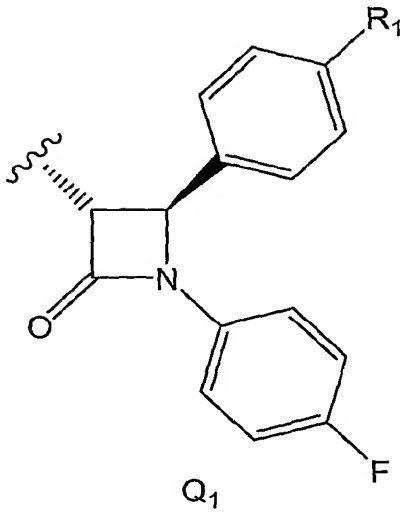
The reduction can be performed in a suitable solvent selected from hydrocarbons, chlorinated hydrocarbons, alkyl ethers, nitriles, dipolar aprotic solvents, cyclic ether or mixtures thereof. The cyclic ether can be dioxane, tetrahydrofuran or mixtures thereof. The compound of Formula II can be added to (-)-B-chlorodiisopinocampheylborane at a temperature from about -80 °C to about 40 °C. The reaction can be carried out at the temperature of from about -80 °C to about 45 °C.

Also provided herein are processes for preparing ezetimibe comprising the step of deprotecting a compound of Formula I



Formula I

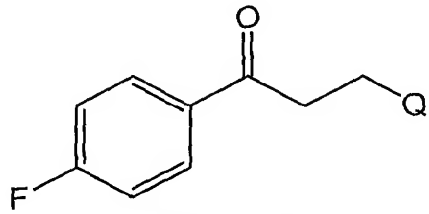
wherein Q can be Q_1



Q_1

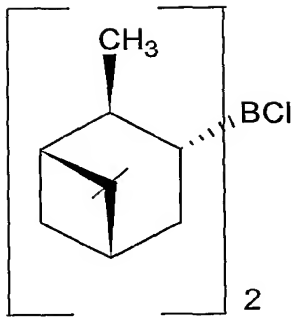
and wherein R_1 can be a protected hydroxy group.

The compound of Formula I can be prepared by reducing a compound of Formula II,



Formula II

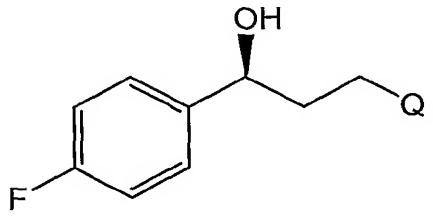
with (-)-B-chlorodiisopinocampheylborane of Formula III.



Formula III

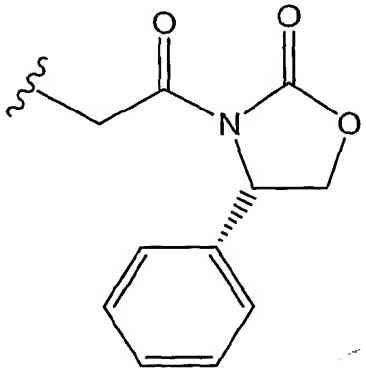
Also provided herein are processes for preparing ezetimibe comprising the steps of

a. reacting a compound of Formula I



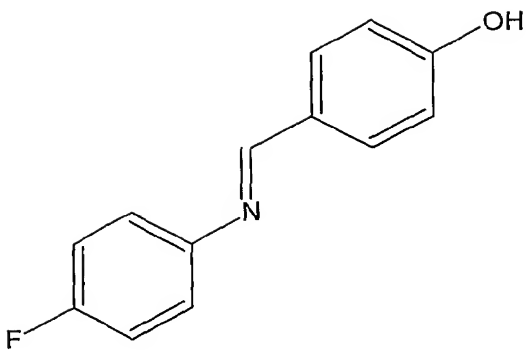
Formula I

wherein Q can be Q_2



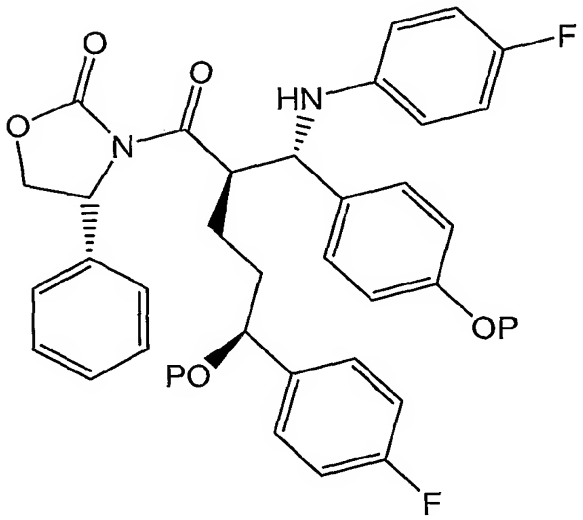
Q_2

with an imine of Formula IV



Formula IV

and at least one hydroxy protecting agent to form the (β-substituted-amino) amide of Formula V,



Formula V

wherein P can be a protecting group,

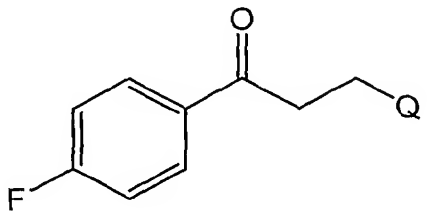
b. reacting the hydroxy-protected (β-substituted-amino) amide with i) a silylating agent and a fluoride ion catalyst cyclizing agent; ii) a silylating agent and a quaternary ammonium salt of a chiral auxillary, or iii) a strong non-nucleophilic base, and

c. removing the hydroxy protecting group.

The hydroxy protecting agent can be chloromethylsilane, chlorotrimethylsilane, tert-butyldimethylsilyl chloride, or a mixture thereof. The silylating agent can be bistrimethylsilyl acetamide. The fluoride ion catalyst cyclizing agent can be

tetrabutylammonium fluoride trihydrate. The chiral auxillary can be (4S)-4-phenyl-2-oxazolidinone.

In one embodiment, compounds of Formula I can be prepared by reducing a compound of Formula II,

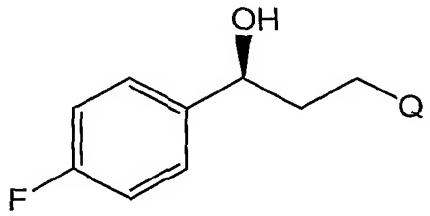


Formula II

with (-)-B-chlorodiisopinocampheylborane.

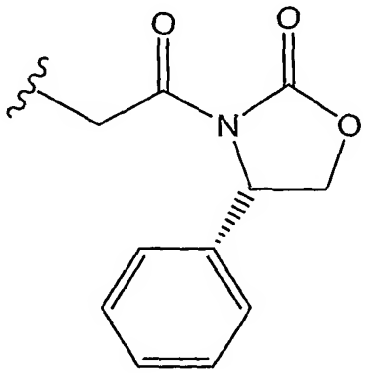
Also provided herein are compounds prepared by processes comprising the steps of:

a. reacting a compound of Formula I



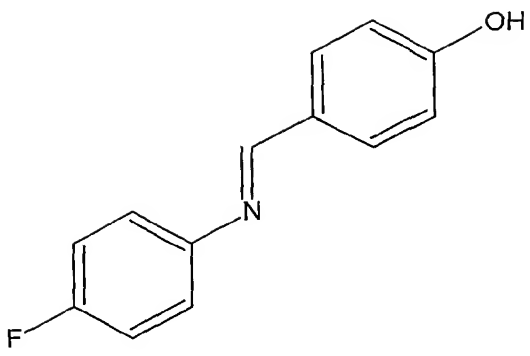
Formula I

wherein Q is Q_2



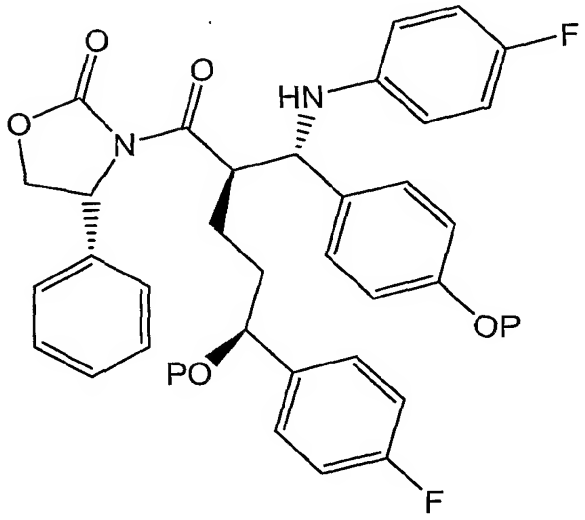
Q_2

with an imine of Formula IV



Formula IV

and at least one hydroxy protecting agent to form the (β-substituted-amino) amide of Formula V



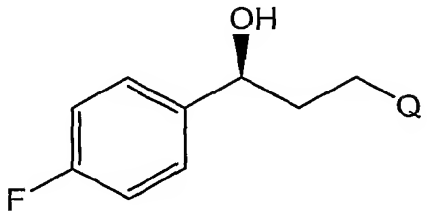
Formula V

wherein P is a protecting group,

b. reacting the hydroxy-protected (β-substituted-amino) amide with i) a silylating agent and a fluoride ion catalyst cyclizing agent; ii) a silylating agent and a quaternary ammonium salt of a chiral auxillary, or iii) a strong non-nucleophilic base, and

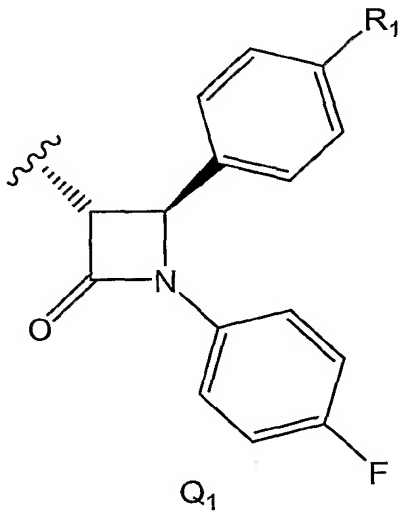
c. removing the hydroxy protecting group.

Also provided herein are compounds prepared by processes comprising the step of deprotecting a compound of Formula I



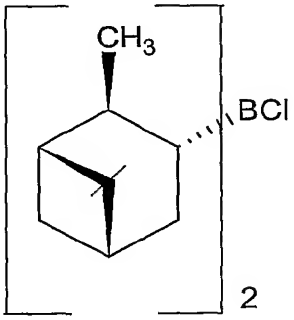
Formula I

wherein Q is Q_1



Q_1

and wherein R_1 is a protected hydroxy group.



Formula III

Detailed Description of the Invention

Compounds of Formula II, wherein Q represents Q_1 may be obtained by known process, including, for example, processes disclosed in U.S. Patent Nos. 5,886,171 and 5,856,473, which are incorporated herein by reference. For example, compounds of Formula II may be obtained by alkylating (4S)-1-(4-fluorophenyl)-4-(4-substituted phenyl) azetidin-2-one with 4-fluorocinnamyl bromide, followed by oxidation.

Compounds of Formula II, wherein Q represents Q_2 may be obtained by known processes including, for example, processes disclosed in U.S. Patent No. 6,207,822, which is incorporated herein by reference. For example, Compounds of Formula II may be obtained by reacting p-fluorobenzoylbutyric acid with pivaloyl chloride and reacting the product with a chiral auxillary, (4S)-4-phenyl-2-oxazolidinone.

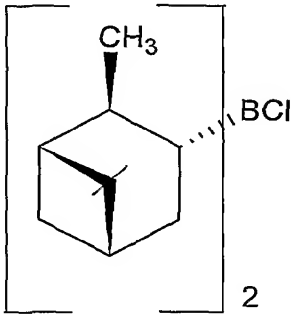
Compounds of Formula II, wherein Q represents Q_3, may be obtained by esterification of the corresponding acid, which in turn may be prepared by known processes including, for example, processes disclosed in U.S. Patent No. 6,207,822, which is incorporated herein by reference. The corresponding acid may be obtained by reacting glutaric anhydride and fluorobenzene in the presence of aluminum chloride.

(-)-B-chlorodiisopinocampheylborane is commercially available as a solid or a solution in heptane.

The reaction of compound of Formula II, wherein Q is as defined above, with (-)-B-chlorodiisopinocampheylborane may carried out in the presence of a suitable solvent. Suitable solvents are inert organic solvents that do not change under the reaction conditions. Examples of such solvents include hydrocarbons such as benzene, xylene, toluene, hexane, cyclohexane, heptane and octane; chlorinated hydrocarbons such as methylene chloride, ethylene dichloride and carbon tetrachloride; alkyl ethers such as diethylether, diisopropylether and dimethoxyethane; nitriles such as acetonitrile and benzonitrile; dipolar aprotic solvents such as dimethylsulfoxide and dimethylformamide; cyclic ethers such as dioxane and tetrahydrofuran; and mixtures thereof.

It has been observed that the dilution of the reaction affects the enantioselectivity. The reaction carried out at high concentration, results in high selectivity and the selectivity decreases with increase in dilution.

The compound of Formula II, wherein Q is as defined above, may be reacted with (-)-B-chlorodiisopinocampheylborane (Formula III)



Formula III

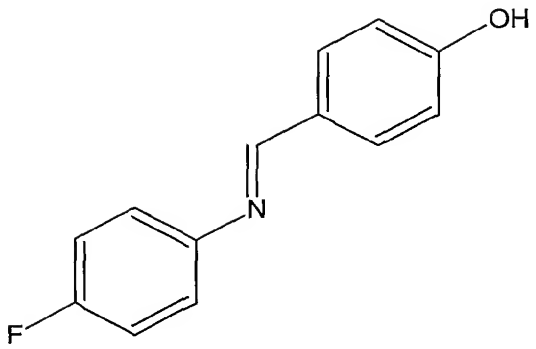
at a temperature range of about -80 °C to about 40 °C in a suitable solvent, and in some particular embodiments, the temperature may range from about -40 °C to about 10 °C. The reaction of compound of Formula II with (-)-B-chlorodiisopinocampheylborane may carried out at the temperature range of about -80 °C to about 45 °C.

In some particular embodiments, the reaction may be quenched by adding a dialkanolamine, for example, diethanolamine, dipropanolamine, dibutanolamine or mixtures thereof.

Compounds of Formula I, wherein Q is as defined above, can be converted to ezetimibe, by disclosed methods including, for example, methods disclosed in U.S. Patent Nos. 6,207,822; 5,886,171; and 5,856,473 and pending Indian Patent Application No. 668/DEL/2003 (PCT Patent Application WO 2004/099132 A2), which are incorporated herein by reference.

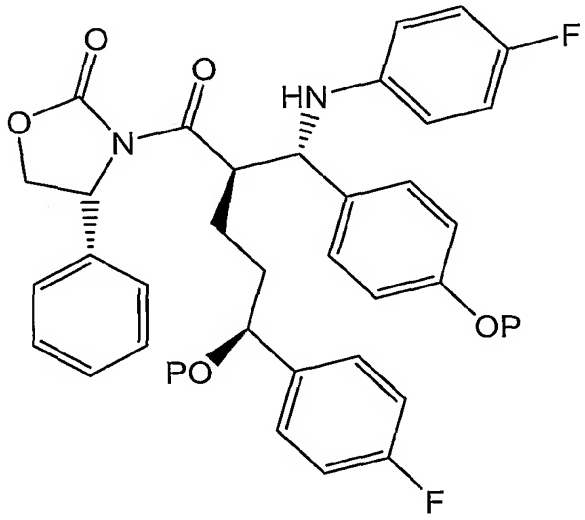
Compounds of Formula I, wherein Q is Q_1 and R_1 is a protected hydroxy group, can be converted to ezetimibe by removal of protecting group, for example, by hydrogenation to remove a benzylic protecting group.

The compound of Formula I, wherein Q is Q_2, can be converted to ezetimibe by reacting the compound of Formula I, wherein Q is Q_2 with an imine of Formula IV



Formula IV

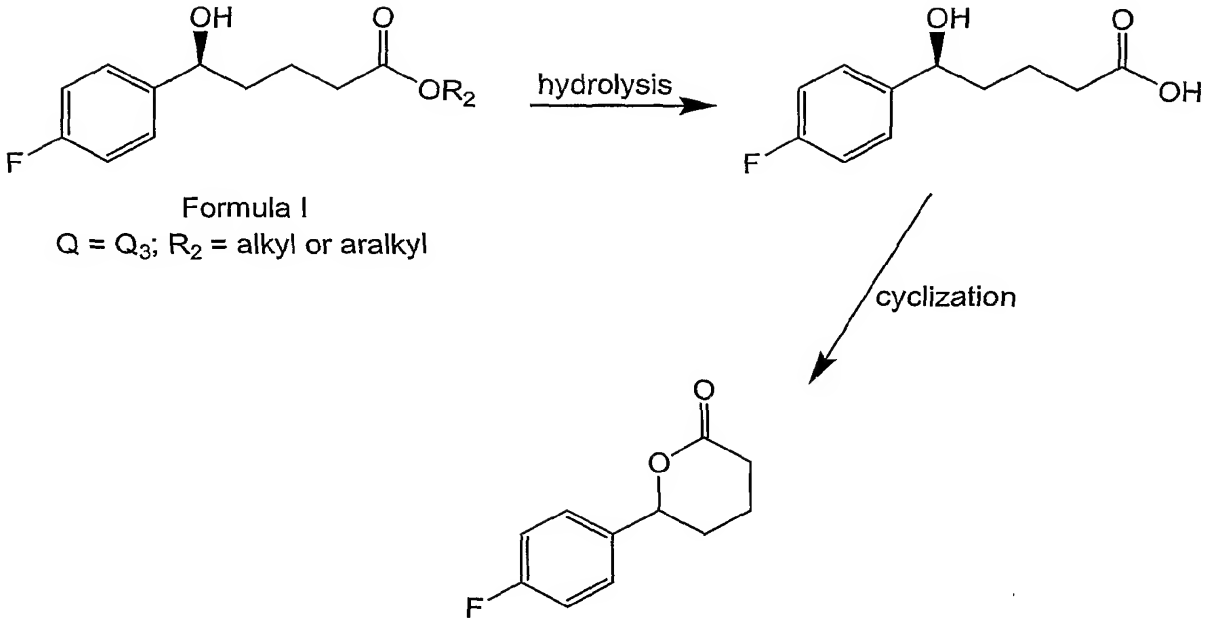
and a hydroxy protecting agent to obtain (β-substituted-amino) amide of Formula V,



Formula V

which is then reacted with a silylating agent and a fluoride ion catalyst cyclizing agent; a silylating agent and a quaternary ammonium salt of a chiral auxillary, (4S)-4-phenyl-2-oxazolidinone; or a strong non-nucleophilic base followed by removal of hydroxy protecting group to yield ezetimibe. In some particular embodiments hydroxy protecting group, silylating agent and fluoride ion catalyst cyclizing agent are chlorotrimethylsilane, bistrimethylsilyl acetamide and tetrabutylammonium fluoride trihydrate respectively.

Compounds of Formula I, wherein Q is Q_3, can be converted to ezetimibe by methods disclosed in PCT Application No. WO 2004/099132. For example, a compound of Formula I can be hydrolyzed to the corresponding acid, which is then cyclized to obtain the corresponding chiral delta lactone, as shown in the scheme below.



Formula I
Q = Q_3; R_2 = alkyl or aralkyl

delta lactone

The chiral delta lactone is then reacted with diphenyl imine of Formula IV in the presence of a strong base. The hydrolysis can be carried out in the presence of at least one acid or base. Examples of acids include organic acids, for example, carboxylic acids (*e.g.*, formic acid, acetic acid, propionic acid or mixture thereof), and inorganic acids, for example, hydrochloric acid, hydrobromic acid or mixtures thereof. Examples of bases include alkali metal carbonates (*e.g.*, lithium carbonate, sodium carbonate, potassium carbonate, or mixtures thereof) and hydroxides (*e.g.*, sodium hydroxide, potassium hydroxide, or mixtures thereof). In some embodiments when R_2 is benzyl, hydrogenation in the presence of a metal catalyst (*e.g.*, palladium on carbon and ammonium formate) can be used to form the corresponding acid.

The cyclization reaction after hydrolysis can be carried out in the presence of an acid or a salt of a weak base to obtain a chiral delta lactone. Organic and inorganic acids can be used. Examples of suitable acids include hydrochloric, p-toluenesulfonic, acetic, and methanesulfonic acids. Examples of suitable salts of a weak base include pyridinium p-toluenesulfonate, pyridine hydrobromide or mixtures thereof. The cyclization reaction may be carried out at a temperature range from about –20 °C to about 120 °C, from about 0 °C to about 60 °C, and even from about 10 °C to about 40 °C. Organic solvents can be used in the cyclization reactions, examples of which include, ethers (*e.g.*, diethyl ether,

dibutyl ether, methyl tert-butyl ether, dioxane, tetrahydrofuran or mixtures thereof); chlorinated hydrocarbons (*e.g.*, methylenedichloride, ethylenedichloride or mixtures thereof); esters (*e.g.*, ethyl acetate, isopropyl acetate or mixtures thereof); ketones (*e.g.*, acetone, methylisobutylketone (MIBK) or mixtures thereof); hydrocarbons (*e.g.*, hexane, toluene, xylene or mixtures thereof); acetonitrile; dipolar aprotic solvents (*e.g.*, dimethylformamide, dimethyl sulphoxide, N-methylpyrrolidone, sulfolane or mixtures thereof); or mixtures thereof.

The compound of Formula I, wherein Q is Q_3, can be converted to compound of Formula I, wherein Q is Q_2, by hydrolyzing to the corresponding acid, reacting with pivaloyl chloride and reacting the product with a chiral auxillary, (4S)-4-phenyl-2-oxazolidinone.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are included within the scope of the present invention.

In the following section, embodiments are described by way of examples to illustrate the process of invention. However, these do not limit the scope of the present invention. Several variants of these examples would be evident to persons ordinarily skilled in the art.

EXAMPLES

Example 1: Preparation of (5*S*)-5-(4-fluorophenyl)-5-hydroxypentanoic acid

A solution of methyl 5-(4-fluorophenyl)-5-oxopentanoate (20.57 g, 91.8 mmol) in tetrahydrofuran (42 mL) was added to a stirred suspension of (-)-B-chlorodiisopinocampheylborane (50.07 g, 156.1 mmol) in tetrahydrofuran (50 mL) at a temperature from about -35 °C to -25 °C over 30 minutes. The resulting solution was stirred for 20 hours at -25 °C. The reaction mixture was quenched with water (43 mL) at -10 ± 2 °C over 10 minutes followed by addition of 5M sodium hydroxide solution (123 mL) at 0 °C over 15 minutes. After about 80 minutes, saturated sodium bicarbonate solution (82 mL) and dichloromethane (133 mL) were added. After stirring at about 20 °C for 15 minutes, the two layers were separated. The aqueous layer was acidified with

aqueous 6M hydrogen chloride (25mL) to pH 2.78 and the separated solid was filtered and dried under vacuum to yield (5*S*)-5-(4-fluorophenyl)-5-hydroxypentanoic acid

Yield: 16.25 g

m.p.: 103.3 °C

Enantiomeric purity: 98.36% (by HPLC)

α_D: -24.5° (c = 0.5% in methanol)

Example 2: Preparation of 3-[(5*S*)-5-(4-fluorophenyl)-5-hydroxypentanoyl]-4(S)-4-phenyl-1,3-oxazolidin-2-one

3-[5-(4-fluorophenyl)-5-oxopentanoyl]-4(S)-4-phenyl-1,3-oxazolidin-2-one (100g, 0.281 mol) was added to a solution of (-)-B-chlorodiisopinocampheylborane (180 g, 60 to 65 % by weight solution in heptane, 0.34 mol) in tetrahydrofuran (200 mL) at about 5 °C to about 10 °C under nitrogen atmosphere. The temperature was raised to about 25 °C to 30 °C and the reaction mixture was stirred for 60 minutes. The reaction was monitored by thin layer chromatography (Ethyl acetate:Toluene of 3:7). The reaction mixture was cooled to about 10 °C and diethanolamine (77 g, 0.73 mol) was added slowly while maintaining the temperature below about 25 °C. The reaction mixture was then stirred for 2 hours at 20°C to 30°C and filtered. The precipitate was washed with toluene (500 mL) and the combined filtrate was washed twice with water (400 mL each washing). The organic layer was concentrated under vacuum at about 40 °C to about 45 °C and the residue was triturated with hexane (800 mL). The hexane solution was decanted and concentrated under vacuum to yield the title product as an oil.

Yield: 99.8 g

Enantiomeric purity: 95.59% (by HPLC)

Example 3: Preparation of 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone (Ezetimibe)

A solution of (-)-B-chlorodiisopinocampheylborane in heptane (46 mL, 60-65%) was added slowly to 1-(4-fluorophenyl)-3(R)-[3-oxo-3-(4-fluorophenyl)propyl)]-4-(S)-(4-hydroxyphenyl)-2-azetidinone (20 g, 49 mmol) in tetrahydrofuran (60 mL) at about 5-10 °C. The mixture was brought to ambient temperature (about 25-30 °C) and stirred for 6-8

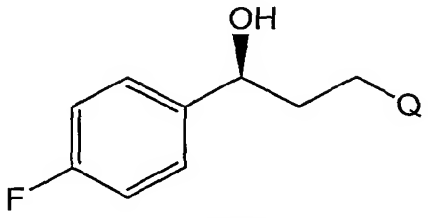
hours until completion of the reduction reaction. The mixture was again cooled and diethanolamine (7.7 g) was added at about 5-10 °C and stirred for about 2 hours. Solid byproducts were filtered and the filtered cake was washed with tetrahydrofuran (20 mL). The filtrate was combined and concentrated on rotary evaporator at about 40 °C. The concentrated mass was dissolved in ethyl acetate (120 mL) and shaken twice with 5% aqueous solution of diethanolamine (30 mL each). The ethyl acetate layer was then washed twice with water (20 mL each) and concentrated. The residue was subjected to column chromatography on silica gel. The product was eluted using ethyl acetate–hexane (40:60 v/v). Product rich fractions were concentrated and the obtained crude product was dissolved in isopropanol (15 mL) at about 50-60 °C to obtain a clear solution. Water (0.9 mL) was added with stirring. The solution was stirred overnight at about 5-10 °C to form a precipitate of the title compound, which was filtered, washed with cold aqueous isopropanol and dried.

Yield: 3 g

Enantiomeric purity: 98.5 % (by HPLC)

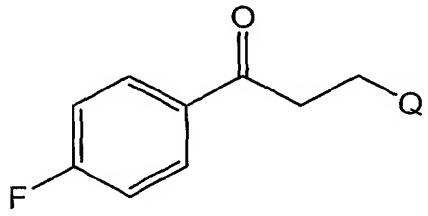
We Claim:

1. A process for the preparation of a compound of Formula I,



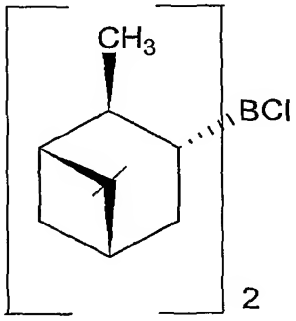
Formula I

comprising reducing the compound of Formula II,



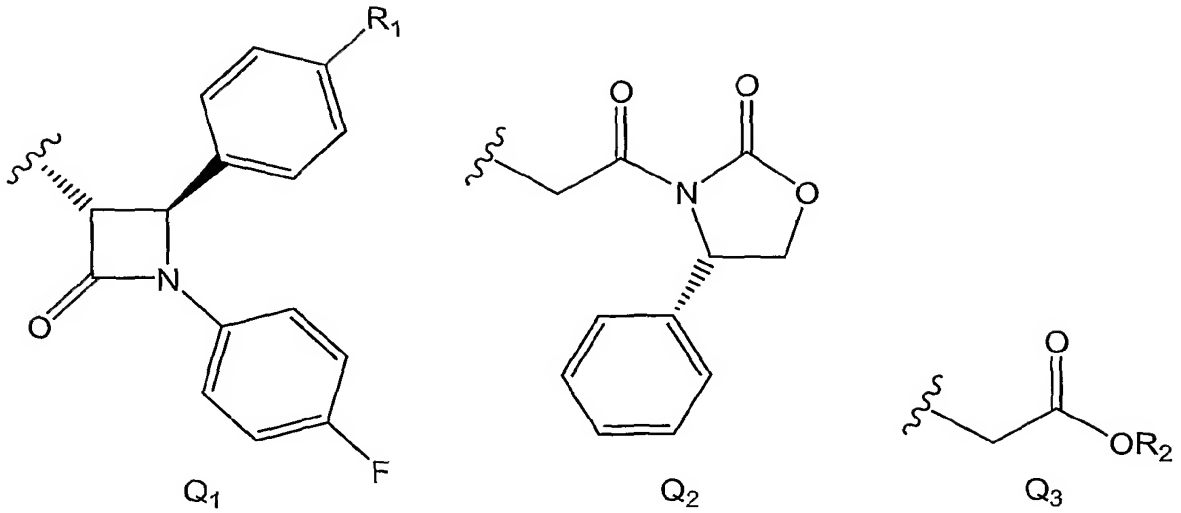
Formula II

with (-)-B-chlorodiisopinocampheylborane of Formula III,



Formula III

wherein Q is Q_1, Q_2, or Q_3,



wherein R_1 is hydroxy or a protected hydroxy group and R_2 is an alkyl, aryl or aralkyl group.

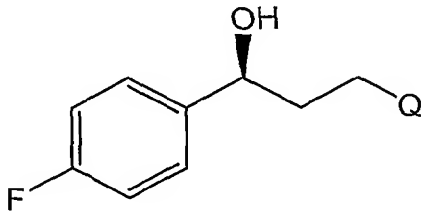
2. The process according to claim 1, wherein the reduction is performed in a suitable solvent selected from hydrocarbons, chlorinated hydrocarbons, alkyl ethers, nitriles, dipolar aprotic solvents, cyclic ether or mixtures thereof.

3. The process according to claim 2, wherein cyclic ether is dioxane, tetrahydrofuran or mixtures thereof.

4. The process according to claim 1, wherein a compound of Formula II is added to (-)-B-chlorodiisopinocampheylborane at a temperature from about -80 °C to about 40 °C.

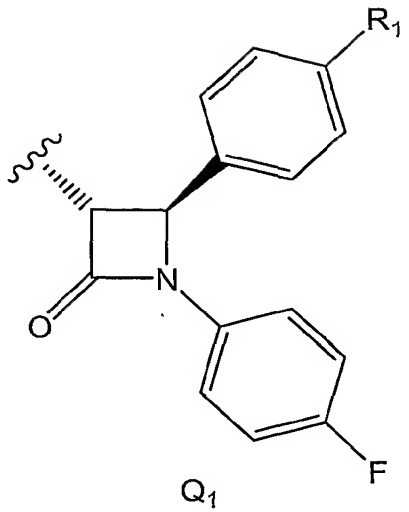
5. The process according to claim 1, wherein the reaction is carried out at the temperature of from about -80 °C to about 45 °C.

6. A process of preparing ezetimibe comprising the step of deprotecting a compound of Formula I



Formula I

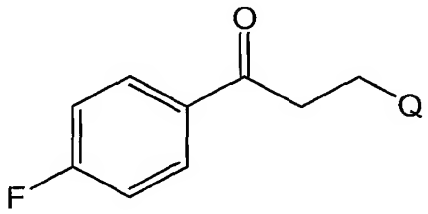
wherein Q is Q_1



Q_1

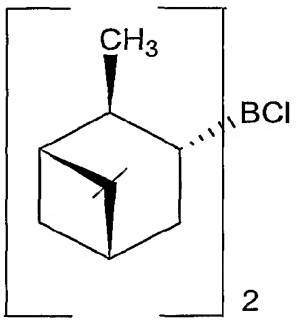
and wherein R_1 is a protected hydroxy group.

7. The process of claim 6, wherein the compound of Formula I is prepared by reducing a compound of Formula II,



Formula II

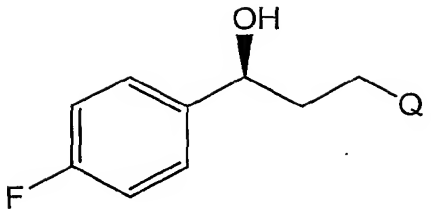
with (-)-B-chlorodiisopinocampheylborane of Formula III.



Formula III

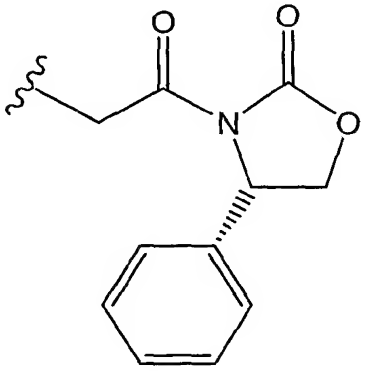
8. A process of preparing ezetimibe comprising the steps of

a. reacting a compound of Formula I



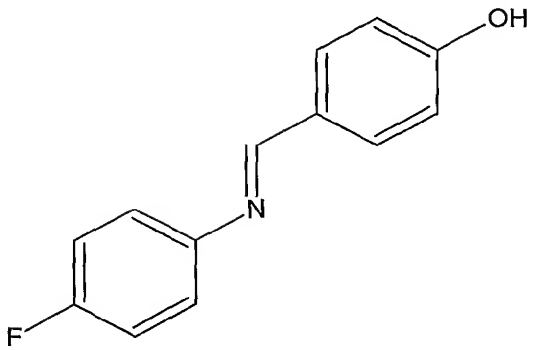
Formula I

wherein Q is Q_2



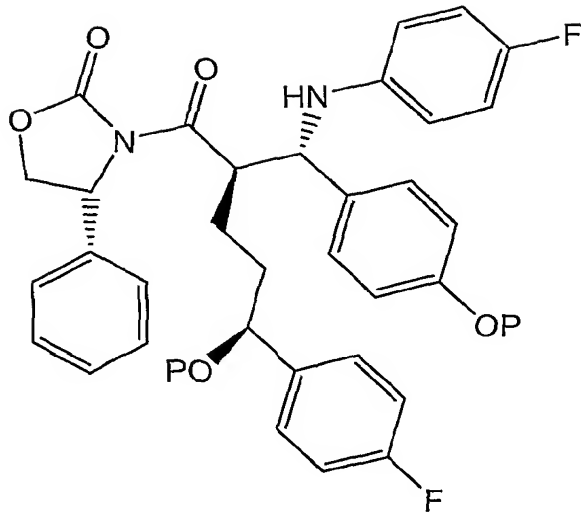
Q_2

with an imine of Formula IV



Formula IV

and at least one hydroxy protecting agent to form the (β-substituted-amino) amide of Formula V



Formula V

wherein P is a protecting group,

d. reacting the hydroxy-protected (β-substituted-amino) amide with i) a silylating agent and a fluoride ion catalyst cyclizing agent; ii) a silylating agent and a quaternary ammonium salt of a chiral auxillary, or iii) a strong non-nucleophilic base, and

e. removing the hydroxy protecting group.

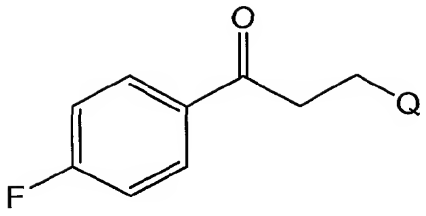
9. The process according to claim 8, wherein the hydroxy protecting agent is chloromethylsilane, chlorotrimethylsilane, tert-butyldimethylsilyl chloride, or a mixture thereof.

10. The process according to claim 8, wherein the silylating agent is bistrimethylsilyl acetamide.

11. The process according to claim 8, wherein the fluoride ion catalyst cyclizing agent is tetrabutylammonium fluoride trihydrate.

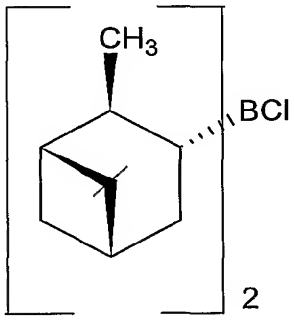
12. The process according to claim 8, wherein chiral auxillary is (4S)-4-phenyl-2-oxazolidinone.

13. The process of claim 8, wherein the compound of Formula I is prepared by reducing a compound of Formula II,



Formula II

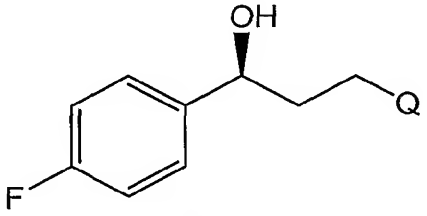
with (-)-B-chlorodiisopinocampheylborane of Formula III.



Formula III

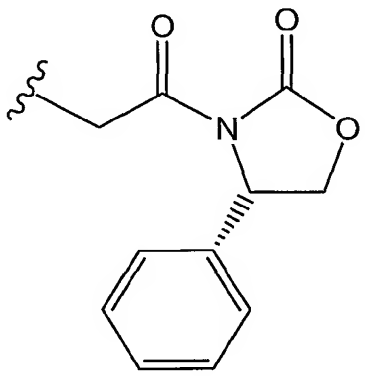
14. A compound prepared by a process comprising the steps of:

a. reacting a compound of Formula I



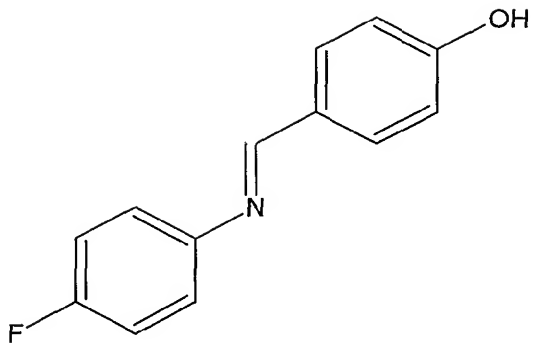
Formula I

wherein Q is Q_2



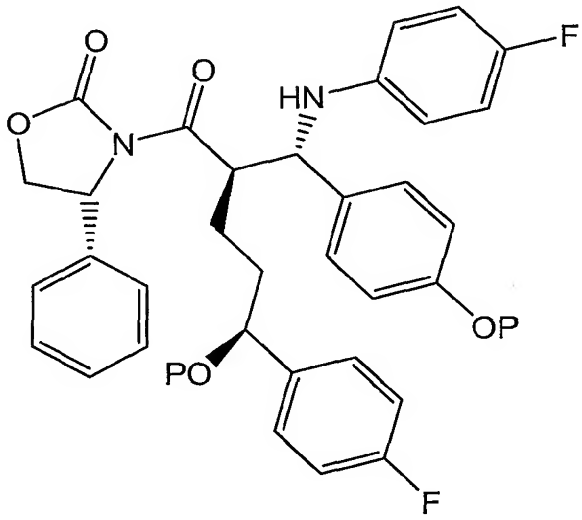
Q_2

with an imine of Formula IV



Formula IV

and at least one hydroxy protecting agent to form the (β-substituted-amino) amide of Formula V



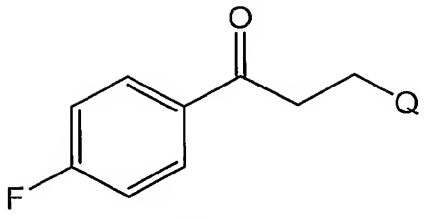
Formula V

wherein P is a protecting group,

b. reacting the hydroxy-protected (β-substituted-amino) amide with i) a silylating agent and a fluoride ion catalyst cyclizing agent; ii) a silylating agent and a quaternary ammonium salt of a chiral auxillary, or iii) a strong non-nucleophilic base, and

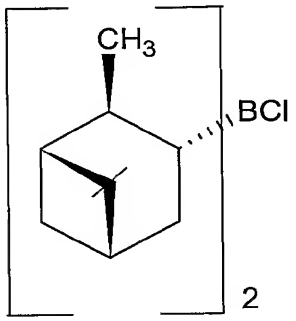
c. removing the hydroxy protecting group.

15. The compound of claim 14, wherein the compound of Formula I is prepared by reducing a compound of Formula II,



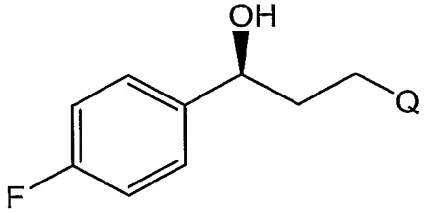
Formula II

with (-)-B-chlorodiisopinocampheylborane of Formula III.



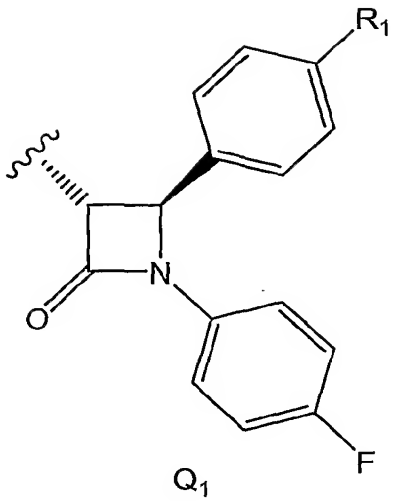
Formula III

16. A compound prepared by a process comprising the step of deprotecting a compound of Formula I



Formula I

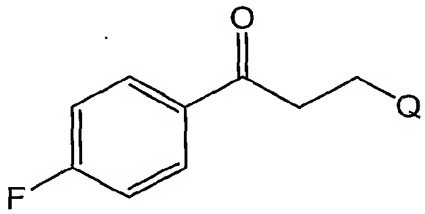
wherein Q is Q_1



Q_1

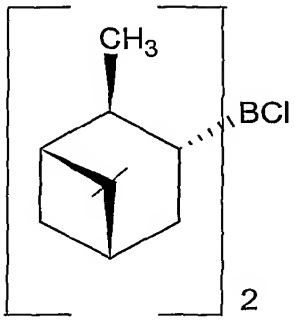
and wherein R_1 is a protected hydroxy group.

17. The compound of claim 16, wherein the compound of Formula I is prepared by reducing a compound of Formula II,



Formula II

with (-)-B-chlorodiisopinocampheylborane of Formula III.



Formula III